Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction

Any of the following laboratory abnormalities:

a. Absolute neutrophil count (ANC) <750 cells/mm3 (0.75×109/L) unless there is documented bone marrow involvement

b. Platelet count <50,000 cells/mm3 (50×109/L) independent of transfusion support unless there is documented bone marrow involvement

c. Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥3.0 upper limit of normal (ULN)

d. Creatinine >2.0×ULN

Example 17: Assay of Drug Combinations

Combinations of a Btk inhibitor and additional cancer treatment agents were assayed using DoHH2 cells.

DOHH2 is a DLBCL (diffuse large B-cell lymphoma) cell line, from a transformed follicular lymphoma patient. It is moderately sensitive to a Btk inhibitor.

The Btk inhibitor was incubated with other cancer drugs for 2 days. Assay was an alamar blue assay.

The combinations were:

a. Btk inhibitor and Gemicitabine;

b. Btk inhibitor and Dexamethasone;

c. Btk inhibitor and Lenalinomide;

d. Btk inhibitor and R-406;

e. Btk inhibitor and Temsirolimus;

f. Btk inhibitor and Carboplatin;

g. Btk inhibitor and Bortezomib; and

h. Btk inhibitor and Doxorubicin.

Results are presented in FIGS. **28-31**.

Example 18: Assay of Drug Combinations

Combinations of a Btk inhibitor and additional cancer treatment agents were assayed using TMD8 cells.

TMD8 is a NF-kB signalling-dependent ABC-DLBCL cell line. It is sensitive to BTK inhibitors alone at low nanomolar concentrations (GI50~1-3 nM). A Btk inhibitor was incubated with other cancer drugs for 2 days. Assay was an alamar blue assay.

The combinations were:

a. Btk inhibitor and CAL-101;

b. Btk inhibitor and Lenalinomide;

c. Btk inhibitor and R-406;

d. Btk inhibitor and Bortezomib;

e. Btk inhibitor and Vincristine;

f. Btk inhibitor and Taxol;

g. Btk inhibitor and Fludarabine; and

h. Btk inhibitor and Doxorubicin.

Results are presented in FIGS. **32-39**.

Example 19: Clinical Trial of Btk Inhibitor in Combination with BR

A clinical trial was performed to determine the effects of combining a Btk inhibitor with BR (bendamustine and rituximab). The Btk inhibitor was administered. Following an increase in the concentration of lymphoid cells in the peripheral blood, BR was administered. Initial results indicated that the combination of the Btk inhibitor and BR resulted in substantially no lymphoid cells in the peripheral blood.

Example 20: Clinical Trial of Btk Inhibitor in Combination with Ofatumumab

A clinical trial was performed to determine the effects of combining a Btk inhibitor with ofatumumab. The Btk inhibitor was administered. Following an increase in the concentration of lymphoid cells in the peripheral blood, ofatumumab was administered. Initial results indicated that the combination of the Btk inhibitor and ofatumumab resulted in a decrease in lymphoid cells in the peripheral blood.

SEQUENCE LISTING

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<223> OTHER INFORMATION: Btk Peptide Substrate

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1 5 10 15

What is claimed is:

1. A method of inhibiting proliferation and survival of activated B-cells in a human subject suffering from a B-cell proliferative disorder, comprising: orally administering to the human subject suffering from a B-cell proliferative disorder a therapeutically effective amount of 1-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one (Compound 13), on a continuous once-daily regimen until progression of the disorder or unacceptable toxicity,

wherein said administration of the therapeutically effective amount results in an $AUC_{(0-24)}$ of >about 100 ng*h/ml; and

wherein said administration of the therapeutically effective amount results in >90% of the Btk active sites in the peripheral blood mononuclear cells of the human subject being occupied by Compound 13 twenty-four hours following said administration.

2. The method of claim **1**, wherein the once daily regimen is continued for at least 6 months.